

A comparison of attrition rates in patients undergoing sublingual immunotherapy vs subcutaneous immunotherapy

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Background: Effective allergy immunotherapy (IT) requires patient compliance. Numerous studies have shown high noncompliance rates in patients undergoing IT. For patients enrolled in subcutaneous IT (SCIT), noncompliance rates were noted to range from 11% to 50%, whereas sublingual IT (SLIT) patients had noncompliance rates ranging from 3% to 25%. Comparing noncompliance rates is difficult because noncompliance in SCIT is defined as withdrawal from therapy, whereas in SLIT it is considered poor adherence to daily administration. The aim of this study was to compare attrition rates in patients enrolled in SCIT vs SLIT, as well as major factors leading to termination of IT.

Methods: We retrospectively compared attrition rates, IT duration, and reasons for termination between patients enrolled in SCIT (n = 139) and SLIT (n = 78), over a 4-year period.

Results: Attrition rates for SCIT and SLIT were 45% and 41%, respectively ($p = 0.669$). No significant difference in duration of IT was observed between the groups (≤ 1 month, $p = 0.079$; 1-2 months, $p = 0.486$; 2-3 months, $p = 0.165$; 3-6

months, $p = 0.575$; 6-12 months, $p = 0.361$; 12-24 months, $p = 1.000$; and ≥ 24 months, $p = 0.258$). Among reasons cited for discontinuing IT, SCIT patients reported inconvenience ($p = 0.001$), whereas SLIT patients indicated efficacy concerns ($p = 0.022$) as the major basis for withdrawal.

Conclusion: No significant difference was observed in attrition rates between SCIT and SLIT. While there was no significant difference in duration of IT prior to withdrawal, there was a trend toward earlier withdrawal in SCIT patients. The reasons for withdrawal, however, were considerably different between the 2 groups. © 2012 ARS-AAOA, LLC.

Key Words: noncompliance; adherence; duration; allergic rhinitis; efficacy; immunotherapy

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Allergic rhinitis can have a significant impact on the quality of life, and cause a substantial financial burden to the patient due to the cost of frequent physician visits, missed work days, lower productivity, and medications necessary for symptomatic control. Immunotherapy (IT) is recognized as an effective method of treating allergic rhinitis because it directly addresses the immunoglobulin E (IgE)-mediated immunopathology, not just the symptoms.¹ By gradually administering increasing doses of specific causative allergens, the patient's clinical reactivity is pro-

gressively reduced.² Additionally, IT has the capacity to alter the natural course of allergy allowing for long-lasting efficacy even after the course of IT is completed.³

Effective IT typically requires at least a 3-year treatment course in order to reach appropriate immunologic response and to avoid prompt recurrence of symptoms.² Patient compliance is a major determinant of the long-term efficacy of IT, but prolonged treatment courses can be difficult for patients to endure. Previously published studies have cited high dropout rates and poor patient compliance in patients undergoing IT.^{2,4} Subgroup analyses of various types of IT, including subcutaneous IT (SCIT), which is provided in the physician's office, and sublingual IT (SLIT), which is self-administered at home, suggest higher compliance rates in patients undergoing SLIT due to more convenient administration.² Self-administration allows patients to arrange their allergen extract dosing at a time most convenient for them, as well as decreasing the time associated with traveling to and from the physician's office.

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There is a difference in how noncompliance is defined for SCIT and SLIT patients in the literature.² For SCIT, noncompliance was equated to the discontinuation of IT. But for patients enrolled in SLIT, most studies defined noncompliance as inconsistent self-administration of the allergen extracts. This discrepancy in the definition makes accurate comparison between the 2 groups difficult.

The specific aim of this study was to compare attrition rates in patients enrolled in SCIT vs SLIT. Additionally, we looked at major factors leading to termination of IT, as well as duration of IT prior to withdrawal between the 2 groups.

Materials and methods

Before commencing this study, approval was obtained from the Institutional Review Board. The charts of 217 patients who received IT in the Otolaryngology–Head and Neck Surgery Department of Weill Cornell Medical College from 2007 through 2010 were retrospectively reviewed. Patients were separated into SCIT and SLIT groups depending on the type of IT they received. The number of patients who withdrew from each group and the duration of IT prior to withdrawal were determined. The duration of therapy for SCIT was determined by the length of time receiving injections. The duration of therapy for SLIT was estimated by calculating the number of SLIT vials the patient had received. Vials 1 through 3, which represented the escalation phase of IT, each contained approximately 1 month worth of allergen extract. Each vial after that, corresponding to the maintenance phase, contained approximately 3 months worth of allergen extract. The maintenance treatment vials for SLIT were prepared to deliver approximately 5 to 20 μ g of major antigen protein daily with a maximum daily maintenance dose of 20 μ g of major antigen protein. For SCIT, treatment vials were escalated to provide injections with primarily concentrate and #1 dilutions of each antigen for each maintenance dose, or until a large local reaction required earlier cessation of escalation. An attempt was made to contact each patient who withdrew from IT via telephone to determine the reason they withdrew. The attrition rate, duration of IT, and reason for withdrawal was compared between SCIT and SLIT groups, and the data were analyzed using Fischer's exact test with significance defined as $p < 0.05$.

Results

Patient demographics for the SCIT and SLIT groups are shown in Table 1. Of the 139 patients enrolled in SCIT, 62 patients (45%) withdrew during the 3-year study period; and of the 78 patients enrolled in SLIT, 32 (41%) patients withdrew during this time period. There was no statistically significant difference between the attrition rates between the SCIT and SLIT groups ($p = 0.6694$).

The duration of therapy prior to withdrawal from IT is depicted in Figure 1. There was no significant difference in

TABLE 1. Characteristics (gender, age at initiation of IT, and number of allergens treated) of patients who were enrolled in SCIT and SLIT

	SCIT	SLIT
Number of patients enrolled, n	139	78
Males, n (%)	54 (39)	45 (58)
Females, n (%)	85 (61)	33 (42)
Age range (years)	8–82	6–74
Mean age (years)	36.2	35.1
Mean allergens treated, n	7.5	7.3
Number of patients who withdrew	62	32
Males, n (%)	22 (35)	21 (66)
Females, n (%)	40 (65)	11 (34)
Age range (years)	8–82	8–67
Mean age (years)	36.6	33.4
Mean allergens treated, n	7.1	7.3

IT = immunotherapy; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

duration of IT prior to withdrawal observed between the SCIT and SLIT groups. However, there was a trend toward earlier withdrawal in SCIT patients, with the majority discontinuing within the first 3 months. The majority patients who withdrew from SLIT terminated their therapy later in IT, 2 to 12 months into their IT course.

Reasons for withdrawal from IT are shown in Figure 2. Of the 62 patients who withdrew from SCIT, 32 patients completed a survey regarding reasons for withdrawal; and of the 32 patients who withdrew from SLIT, 8 patients completed this survey. The most common reason for withdrawal in the SCIT group was inconvenience, whereas no patients in the SLIT group withdrew due to inconvenience. Among patients who withdrew from the SLIT group, concern about efficacy was the major basis for withdrawal. Numerous SLIT patients frequently cited financial concerns as the reason for terminating IT. Of SLIT patients who withdrew, 60% was due to financial concerns versus only 11% of SCIT patients; however, the difference between the 2 groups did not reach statistical significance. There were 3 SCIT patients who withdrew secondary to unrelated medical issues (1 patient was trying to conceive, 1 patient was diagnosed with cancer, and 1 patient was starting chemotherapy). There were 2 patients in the SCIT group who withdrew due to adverse reaction; 1 patient had a delayed local reaction with induration and erythema around injection site and the other patient had a delayed reaction with episodes of hives and itchiness. There was 1 patient in the SLIT group who withdrew due to an adverse reaction; the patient reported anxiety, shortness of breath, and palpitations after taking the sublingual drops.

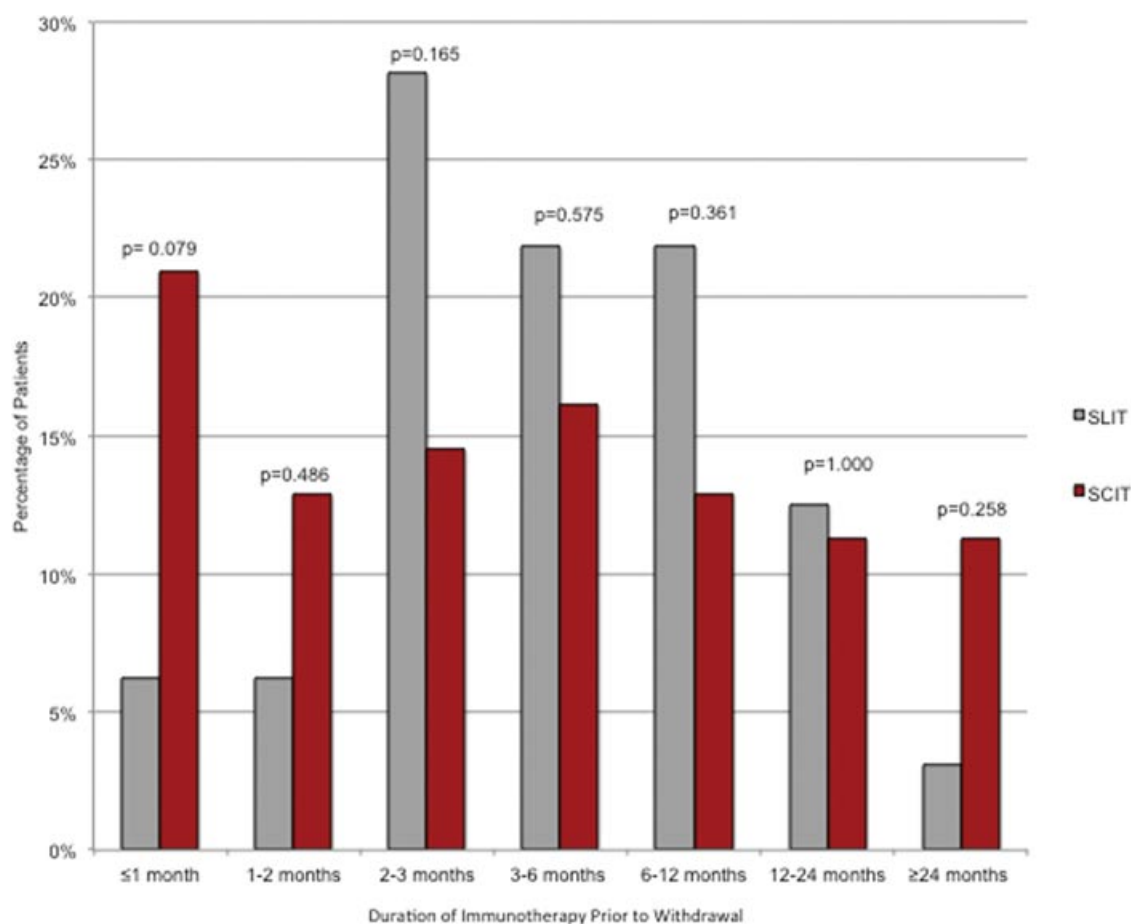


FIGURE 1. Duration of immunotherapy prior to withdrawal. Duration of therapy was broken down into <1 month, 1 to 2 months, 2 to 3 months, 3 to 6 months, 6 to 12 months, 12 to 24 months, and >24 months. Duration of therapy for SCIT was determined by the length of time receiving injections. Duration of therapy for SLIT was estimated by calculating the number of SLIT vials the patient had received. Vials 1 through 3 each contained approximately 1 month of allergen extract, whereas each vial thereafter contained approximately 3 months of allergen extract. The calculation was based on assumption that the patient completed the treatment course through the last vial they received. SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

Discussion

Previous studies have shown noncompliance rates for patients enrolled in SCIT ranging from 11% to 50%, whereas noncompliance rates reported for SLIT patients ranged from 3% to 25%.² It has been suggested that noncompliance rates in patients undergoing SLIT are lower due to less inconvenience of administration. However, noncompliance rates in patients enrolled in SLIT were defined as inconsistent daily extract administration, not actual withdrawal from IT. There is no standard for measuring and reporting compliance rates, and with the discrepancy, it is difficult to accurately compare rates and determinants of compliance.^{5,6}

To the best of our knowledge, there have been no studies specifically comparing the attrition rate of patients enrolled in SCIT and SLIT. Extrapolating from previous compliance studies, one would suspect that attrition rates would be lower in patients undergoing SLIT due to improved convenience and decreased risk of adverse reactions. However, in our study, we found that there was no statistically sig-

nificant difference in the attrition rates between SLIT and SCIT.

Although SLIT does not have the inconvenience of frequent office visits for administration, it has different factors that affect patient adherence and therapy withdrawal. Compliance problems in this group are similar to patients undergoing drug treatments for chronic disease, which were well-described over 30 years ago by Blackwell.⁷ Additionally, poor compliance in patients enrolled in SLIT could also be affected by the erroneous perception that SLIT is no longer needed once allergic symptoms are improved.⁸ These types of misconceptions regarding IT can lead to inconsistency with self-administration and may actually have a significant impact on therapy failure or poor efficacy in patients undergoing SLIT.^{9,10}

When looking at the population demographics between the SCIT and SLIT groups (Table 1), in the SCIT group there is a higher percentage of women enrolled, and in the SLIT group there is a higher percentage of men enrolled. The exact reason for this difference is unclear, but is likely multifactorial, with considerations including the

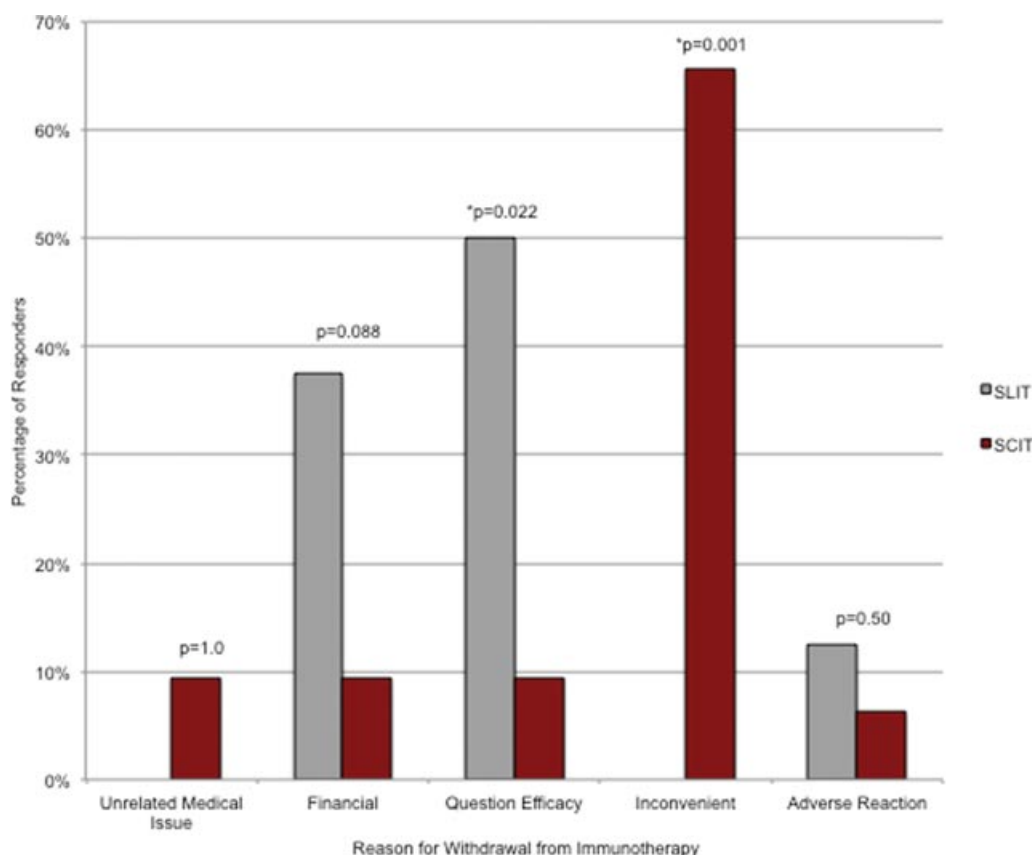


FIGURE 2. Reason for withdrawal from immunotherapy. When surveyed about the reason for withdrawal, patients offered 5 main reasons: unrelated medical issues, financial concerns, questionable efficacy, inconvenience, and adverse reaction. One of these factors was recorded for each patient who provided reason for withdrawal.

patient population registered at the institution as well as socioeconomic factors. However, when comparing the patients within each group (SCIT and SLIT), there was no discrepancy in the attrition rate secondary to gender.

We found no statistically significant difference in duration of IT between the 2 groups. However, a trend was noted that SCIT patients withdrew earlier in their course of IT than SLIT patients. Previous studies on SCIT have shown a consistent rate of withdrawal during the first 3 years of IT.⁴ In our study, the majority of patients who withdrew from SCIT discontinued within in the first 6 months, which was likely secondary to inconvenience of weekly injections during the escalation phase. The majority of patients who withdrew from SLIT, however, terminated their therapy later, up to 12 months into their treatment.⁸

When examining reasons for withdrawal, patients cited inconvenience as the main reason for withdrawal from SCIT, which is consistent with previous literature.^{2,11,12} SLIT patients, however, indicated concerns regarding efficacy of treatment as the major basis for withdrawal. And, whereas patients who withdrew from SLIT frequently indicated financial concerns for discontinuing IT, this factor did not reach statistical significance. Further evaluation with a larger sample size and more extensive follow-up is needed to better determine if financial concerns in SLIT are a significant factor in withdrawal.

There was only a small number of respondents to the telephone survey, particularly in the SLIT group. A frequently encountered reason for nonresponse was that patients had moved away from the local area. Additionally, many patients may not have responded to the survey because they did not feel obligated to answer questions regarding their experience with IT when they were no longer receiving treatment. It is clear that the small number of respondents is a limitation of this part of the analysis and requires further examination with a large respondent population to better evaluate the reasons why patients terminate IT and to determine ways to prevent early treatment withdrawal.

While this study focused mainly on the attrition rates for SCIT and SLIT, it is likely that compliance during IT has a major impact on the course of therapy, both in terms of efficacy as well as attrition rate. If patients are inconsistent with their therapy, it is possible that poor compliance could contribute to what is perceived to be questionable efficacy. Additionally, intensive therapy regimens may be difficult to maintain long-term, which can lead to not only poor compliance but also treatment withdrawal.

Conclusion

Our study showed no significant difference in attrition rates between patients undergoing SCIT and SLIT. Although no

significant difference in duration of IT prior to withdrawal was noted, there was a trend toward earlier withdrawal from treatment in the SCIT patients. Additionally, the reasons for withdrawal were considerably different between the groups; SCIT patients reported inconvenience as the major factor for withdrawal, whereas SLIT patients indicated concerns regarding efficacy of the treatment. Future studies will examine methods for accurately measuring compliance during both forms of IT so that meaningful comparisons can be made. The impact of compliance on the outcome of

IT may then be determined, and high-risk groups for poor compliance and treatment withdrawal can be more easily identified. 🌐

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